PROCESSES FOR PREPARING CALCIUM SALT FORMS OF STATINS

CROSS-REFERENCE TO RELATED APPLICATIONS

IS A DIV. OF 10/222,556 FILED 8/16/02 NOW 6,777,552,

This application claims the benefit of provisional application Serial Number 60/312,812, filed August 16, 2001 and U.S. Patent Application Serial No. 10/037,412, filed October 24, 2001, ~~which claims the benefit of provisional application Serial Number 60/249,319, filed November 16, 2000, all of which are incorporated herein by reference.~~

NOW 6,528,661.

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FIELD OF THE INVENTION

The present invention relates to processes for preparing calcium salt forms of statins.

BACKGROUND OF THE INVENTION

The class of drugs called statins are currently the most therapeutically effective drugs available for reducing low-density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease and thus, statins are used in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis. A high level of LDL in the bloodstream has been linked to the formation of coronary lesions that obstruct the flow of blood and can rupture and promote thrombosis. Goodman and Gilman, The Pharmacological Basis of Therapeutics, page 879 (9th Ed. 1996).

Statins inhibit cholesterol biosynthesis in humans by competitively inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A ("HMG-CoA") reductase enzyme. HMG-CoA reductase catalyzes the conversion of HMG to mevalonate, which is the rate determining step in the biosynthesis of cholesterol. Decreased production of cholesterol causes an increase in the number of LDL receptors and corresponding reduction in the concentration of LDL particles in the bloodstream. Reduction in the LDL level in the bloodstream reduces the risk of coronary artery disease. J.A.M.A. 1984, 251, 351-74.

Currently available statins include lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin and atorvastatin. Lovastatin (disclosed in U.S. Pat. No. 4,231,938) and simvastatin (ZOCOR; disclosed in U.S. Pat. No. 4,444,784 and WO 00/53566) are administered in the lactone form. After absorption, the lactone ring is opened in the liver by chemical or enzymatic hydrolysis, and the active hydroxy acid is generated.